DERIVATIVES OF PIPERAZINE VIII

SYNTHESIS OF SUBSTITUTED PIPERAZINES AND REACTIONS OF PIPERAZINES WITH CONJUGATED SYSTEMS

By

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INTRODUCTION

This dissertation deals with two research problems. The first is concerned with the addition of piperazine and N-phenylpiperazine to conjugated systems. Since the products were found to be unsuited for further work because of their instability, a second research was initiated, that of synthesizing substituted piperazines from aminoalcohols.

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PART I

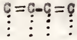
Addition of Piperazines to Conjugate Systems

Discussion of Conjugation

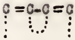
Thiele[1] first pointed out, in 1899, the stability of unsaturated compounds containing two double bonds separated by one single bond. The unsaturation of these systems is limited to the two outer conjugated atoms. In order to explain this phenomenon he supposed that the tendency of double bonds to undergo addition reactions was due to residual affinity and that residual affinities are capable of mutual saturation when double bonds occur in alternate positions to one another. Residual affinities were represented as dotted lines added to the ordinary structural formulae and mutual saturation by uniting two of these lines into a loop.

C=C-C=C

ordinary structural
formula for butadiene



dotted lines
indicating
residual affinity



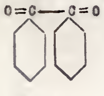
closed loop
indicating
mutual saturation

Systems in which this mutual saturation of residual affinity can occur are described as "conjugated systems".

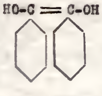
Butadiene is a good example of a conjugated hydrocarbon system. Griner[2] showed that butadiene added bromine to yield a liquid dibromide which on standing soon changed into a solid, M.P. 53-54°. Thiele[1] proved that this solid dibromide was 1,4-dibrom, 2-butene. Much later, Farmer, Lawrence, and Thorpe[3] reinvestigated the addition of bromine to butadiene. They confirmed Griner's observation of the formation of the liquid dibromide and showed it to be 1,2-dibrom, 3-butene. These investigators also showed that the liquid dibromide yields an equilibrium mixture at 100°C. consisting of 20% of the 1,2-isomer and 80% of the 1,4-isomer.

$$CH_2=CH-CH=CH_2 \xrightarrow{Br_2} \begin{array}{ll} CH_2Br\cdot CHBr-CH=CH_2 & 20\% \\ CH_2Br\cdot CH=CH-CH_2Br & 80\% \end{array}$$

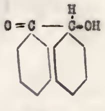
Conjugated systems are not limited to hydrocarbon systems although 1,4-addition to oxygenated systems is more difficult to show since here the addition products tend to rearrange to the 1,2-isomers. Benzil is a good example of this type. The initial reduction product of benzil should be an enol. Actually however benzoin is isolated.



Benzil



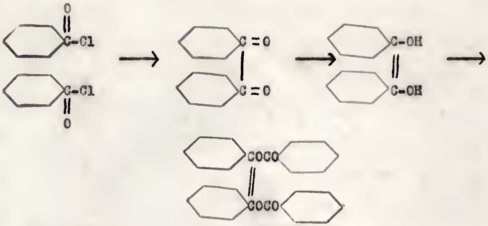
enolic isomer
of benzoin



Benzoin

Although the enolic isomer could not be isolated, Thiele[4] was able to prepare the cis- and trans- forms of the acetate of the enol by carrying out the reduction of benzil in the presence of acetic anhydride and sulfuric acid.

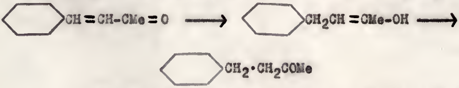
Similarly Klinger[5] was able to prepare the dibenzoate of the enol by the action of sodium amalgam on benzoyl chloride in moist ether.



Another type of conjugated system occurs in the α,β-unsaturated ketones and acids. Ordinarily the ethylenic linkage does not readily unite with hydrogen cyanide, sodium bisulfite or ammonia, which furnish typical reactions with the carbonyl group. When an ethylenic linkage is conjugated with a carbonyl group, however, the addition of these reagents takes place with the ethylenic linkage rather than with the carbonyl group, indicating that the reactivity of the former has been greatly enhanced by conjugation. Thiele pointed out that addition of reagents to this type of conjugated system takes place by addition to the 1,4-atoms rather than to the unsaturated groups separately.

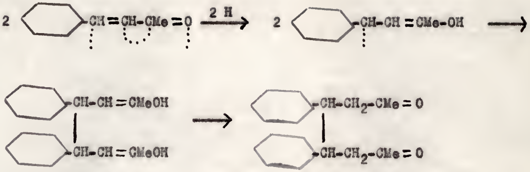
$$CH_2=CH\cdot CH=O \xrightarrow{2\ H} CH_3-CH=CH-OH \longrightarrow CH_3\cdot CH_2CHO$$

$$CH_2=CH\cdot CHO \xrightarrow{HCN} CN\cdot CH_2\cdot CH=CHOH \longrightarrow CN\cdot CH_2\cdot CH_2\cdot CHO$$

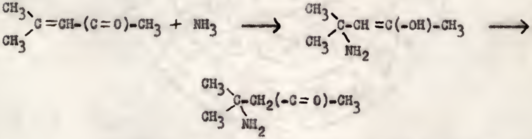


The formation of a β- (but never an α-) compound of the pinacone type as a by-product of this reduction strongly supports the

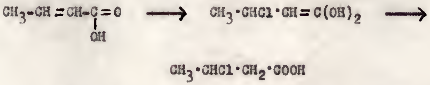
1,4- addition mechanism.



The 1,4-addition hypothesis serves to explain why the ethylenic linkage in α,β-unsaturated ketones and acids appears to possess the unusual property of forming addition-compounds with substances such as ammonia, hydrogen cyanide and sodium bisulfite, which usually unite only with the carbonyl group. For example, mesityl oxide with ammonia yields diacetone amine.

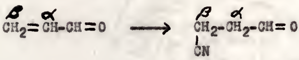


Addition of the hydrogen halides takes place similarly. Crotonic acid combines with HCl to form β-chlorobutyric acid exclusively in direct opposition to Markownikow's[23] rule.



$$CH_3\text{-}CH{=}CH\text{-}\underset{\displaystyle OH}{C}{=}O \longrightarrow CH_3\cdot CHCl\cdot CH{=}C(OH)_2 \longrightarrow CH_3\cdot CHCl\cdot CH_2\cdot COOH$$

Equally important as Thiele's "mutual saturation" hypothesis is Lapworth's [6] conception of alternation, published in 1898, a year before Thiele's original paper. A fundamental characteristic of conjugated systems is the transmission of chemical reactivity from one atom to another. For example, in the addition of hydrogen cyanide to acrolein, the CN-group does not attach itself to the carbon atom of the carbonyl group as it ordinarily does in the formation of a cyanhydrin, but attaches itself to a more remote carbon atom which has become endowed with unusual activity because it is a part of a conjugated system. Similarly, the proton instead of uniting with the oxygen atom attaches itself to a carbon atom.



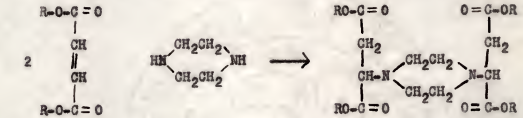
$$\overset{\beta}{CH_2}=\overset{\alpha}{CH}-CH=O \longrightarrow \underset{CN}{\overset{\beta}{CH_2}}-\overset{\alpha}{CH_2}-CH=O$$

The important generalization is that there is an alternation of affinity whereby alternate atoms acquire similar polarities and similar reactivities. "Thus, in the α,β-unsaturated ketones and acids the negative polarity of the oxygen, which enables it to unite to a proton, is transferred to the carbon atom; and the positive polarity of the carbon in the carbonyl group is not shared with the adjacent α- carbon atom (which acquires a negative polarity, as we have seen) but jumps over it and is transferred to the β-carbon atom instead."

Whereas Thiele attributed paired "residual affinities" to all the atoms in the conjugated chain (except the terminal atoms where the residual affinities were unpaired) Lapworth "attributed similar properties only to alternate atoms in the chain, and so provided a firm foundation for all subsequent work on chemical reactivity in conjugated and aromatic systems."[7]

STATEMENT OF RESEARCH PROBLEM

Piperazine, as a cyclic di-secondary amine, should add to α,β-unsaturated ketones and esters. This amine was found to add readily to benzalacetophenone, a typical α,β-unsaturated ketone.[8] Similarly, piperazine added to the conjugated system present in maleic and fumaric esters to yield piperazine-1,4-Bis-(alkyl succinates).[9]

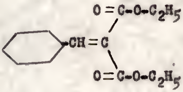


Maleic or fumaric ester   piperazine   piperazino-1,4-Bis-(alkyl succinate)

It was thought desirable to investigate addition products of piperazine and N-phenylpiperazine with arylidenemalonic esters, as such addition compounds might prove interesting and useful starting materials for further research. This investigation constituted the present research.

Previous Studies of the Additions of Amines to Arylidenemalonic Esters

Benzalmalonic ester is the only arylidene malonic ester which has been studied to any extent. This ester exhibits the usual properties of an α, β -unsaturated acid ester as Table I indicates.



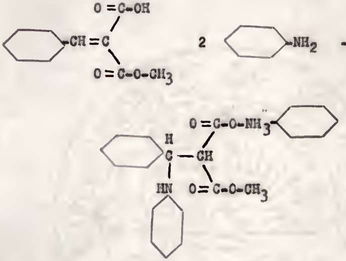
Benzalmalonic ester

TABLE I

Reactions of benzalmalonic ester

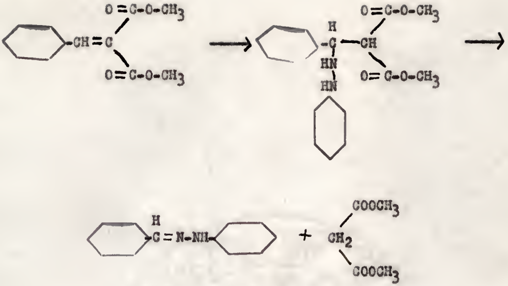
Reagent	Product	Reference
Hydrogen (Al amalgam and water)	Benzylmalonic ester	10
Chlorine or Bromine	Dichloride or Dibromide	11,12
Hydrogen iodide	α-iodobenzylmalonic ester	12
Barium hydroxide and water	Ethanol, Barium salts of benzalmalonic and cinnamic acids	12
Alcoholic KOH	Potassium α-ethoxy-benzylmalonate	12,22
Sodium ethylate	sodio α-ethgaybenzylmalonic ester	13
Hydrogen cyanide	α-cyanbenzylmalonic ester	14
Aniline	α-anilinobenzylmalonic ester	15, 20
Phenylhydrazine	α-(phenylhydrazino) benzyl malonic ester	15, 20
Piperidine	α-piperidinobenzylomalonic ester	16
Methylmagnesium iodide	α-phenethylmalonic ester	17
Phenylmagnesium bromide	benzhydrylmalonic ester	18
Aqueous potassium bisulfite and sulphur dioxide	Sulfonic acid, Potassium salt	19
Aqueous potassium hydroxide	Potassium α-hydroxybenzylmalonate	21

Blank[20] first carried out the addition of an amine to the conjugated system of methyl acid benzalmalonate. The reactàon took place during the course of several hours simply by dissolving the reactants in benzene and allowing the product to crystallize. A small amount of heat was evolved during the reaction.



This addition product was a white, crystalline product meltingat 97.5°. It dissolved to a clear solution in dilute hydrochloric acid. The solution soon clouded and the product smelled of benzaldehyde. Even in moist air the odor of benzaldehyde soon became noticeable.

Similarly, aniline reacted with dimethylbenzalmalonate to yield methyl α-anilinobenzylmalonate and phenylhydrazine gave methyl α-(phenylhydrazino) benzylmalonate. The latter compound melted at 94.5° but on prolonged heating in the dry state or in absolute alcohol solution the addition product decomposed to form malonic ester and benzaldehyde phenyhydrazone.



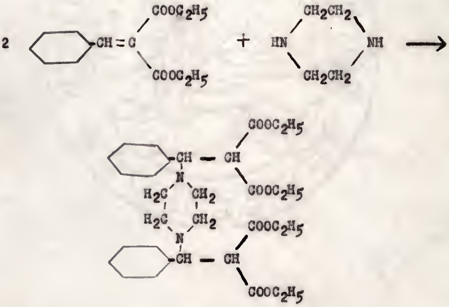
Goldstein[15] found that diethyl α-(phenylhydrazino) benzylmalonate was readily saponified to yield the corresponding potassium salt which was easily soluble in cold water and yielded corresponding insoluble salts with soluble calcium, barium and lead salts. The free acid was unstable, however. An aqueous solution of the potassium salt on treatment with dilute HCl or acetic acid yielded benzaldehyde phenylhydrazone. The addition product of aniline was saponified to yield potassium α-(anilino) benzylmalonate. Its properties were similar to the phenylhydrazine analog. On acidifying, even with carbonic acid, decomposition to aniline, benzaldehyde and malonic acid took place.

Goldstein[16] prepared α-(piperidino) benzylmalonic ester from piperidine and benzalmalonic ester. He obtained the corresponding potassium salt by saponification. The free acid was incapable of existence.

DISCUSSION AND EXPERIMENTAL

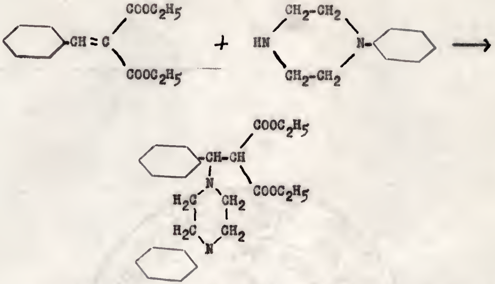
Additions of Piperazine and N-Phenylpiperazine to Arylidenemalonic Esters

The addition of piperazine to diethyl benzalmalonate took place very readily. Equivalent weights of benzalmalonic ester and piperazine were dissolved in alcohol at room temperature. After standing a few hours the mixture became solid. The product was recrystallized from an appropiate solvent and dried. Other arylidenemalonic esters reacted similarly.

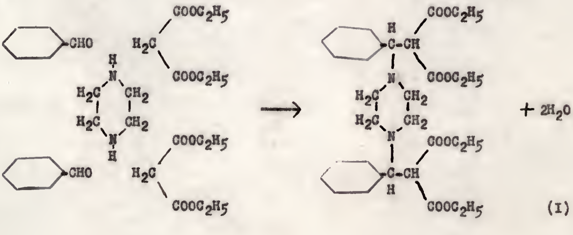


(I)

The product was named tetraethyl (α,α'-diphenyl-1,4-piperazylene dimethylene) dimalonate (hereafter referred to as (I)) at the suggestion of Dr. Austin M. Patterson. No simpler name is available. Similarly, N-phenylpiperazine and benzalmalonic ester yield diethyl α-(4-phenyl-1-piperazyl) benzylmalonate.



Knoevenegal [24] showed that arylidenemalonic esters may be prepared by heating equimolecular quantities of an aromatic aldehyde and malonic ester with a few drops of a secondary amine (usually diethylamine or piperidine) as a catalyst. It occurred to the author that it might be possible to prepare (I) by heating equivalent weights of piperazine, benzaldehyde and malonic ester in alcoholic solution. This proved to be the case. Compound (I) was isolated in equal purity and yield by either method.

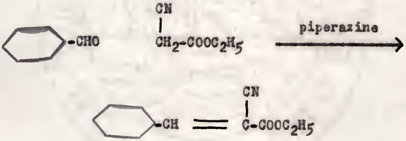


(I)

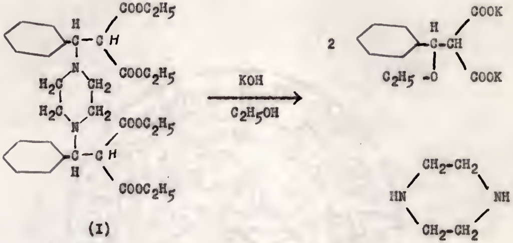
Piperazine and N-phenylpiperazine were reacted with benzal-, piperonal-, p-methoxybenzal-, o-chlorobenzal- and furfural malonic esters. The same compounds resulted on mixing equivalent quantities of the appropriate aldehyde, amine and malonic ester in alcohol.

An attempt was made to react piperazine with the conjugated system present in ethyl α-cyano-β-phenylacrylate (benzalcyanacetic ester) but the amine and ester were recovered unchanged.

Equivalent quantities of benzaldehyde, cyanacetic ester and piperazine yielded benzalcyanacetic ester but no addition product. In this case piperazine served only as a catalyst for condensation of aldehyde with a reactive methylene group.

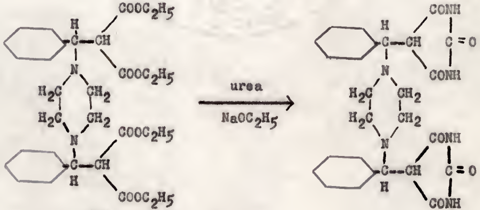


The addition compounds prepared in this research were expected to have properties quite analagous to those prepared by Goldstein,[15,16] from aniline, piperidine and other amines with benzalmalonic ester. However, the saponification of (I) with a slight excess of alcoholic potassium hydroxide did not lead to the expected tetrapotassium (α,α'-diphenyl-1,4 piperazyene dimethylene) dimalonate but yielded a nitrogen-free salt. This was quite surprising since Goldstein obtained the potassium salts of his addition products without difficulty by the same method and did not mention the production of a nitrogen-free salt. The nitrogen-free salt was tentatively identified as potassium α-ethoxybenzylmalonate which could have only been formed by splitting out piperazine, adding alcohol to the conjugated system and hydrolyzing. Piperazine was recovered in good yield from the mother liquid.



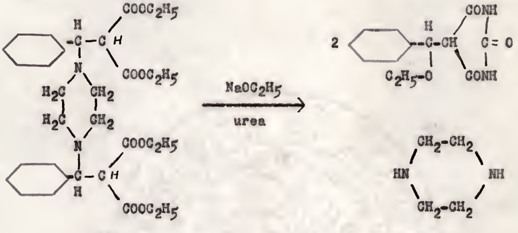
(I)

One object of this research was to prepare a dibarbiturate from (I) by condensing it with urea in the presence of sodium ethoxide.



(I)

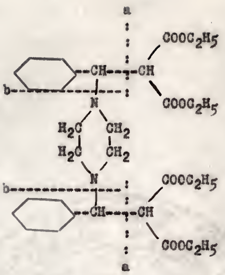
This compound was not produced, however, since in the presence of sodium ethoxide (I) splits out piperazine and adds a molecule of alcohol to the conjugated system. Condensation of this compound with urea leads to α-ethoxybenzylbarbituric acid.



(I)

Acid hydrolysis of (I) resulted in the same type of decomposition as Goldstein[15,16] observed on hydrolyzing the addition products of aniline, piperidine and phenyhydrazine with benzalmalonic ester. Warming (I) for a short time with 3 N hydrochloric acid produced piperazine hydrochloride and benzalmalonic ester. Prolonged hydrolysis yielded benzaldehyde and malonic acid.

The instability of the C—C and C—N linkages of (I) was also indicated by hydrogenolysis experiments. N,N'-Dibenzylpiperazine and malonic ester were produced by cleavage of the C—C bond at (a) and benzylmalonic ester and piperazine were produced by cleavage of the C—N bond at (b). Toluene might be produced by simultaneous cleavage of both bonds but was not identified.



a
COOC₂H₅
CH
CH
b
N
H₂C
CH₂
H₂C
CH₂
N
b
COOC₂H₅
CH
CH
COOC₂H₅
COOC₂H₅
a

(I)

EXPERIMENTAL

MATERIALS. Piperazine hexahydrate, aldehydes and malonic ester were purchased from Eastmen Kodak Co. The arylidenemalonic esters were prepared by the methods of Knoevenagel,[24] Claisen,[26] and Càaisen and Crismer.[12] N-phenylpiperazine was prepared by the method of Pollard and MacDowell.[27]

Preparation of the Condensation Products

METHOD A. One equivalent of the secondary amine was added to 1 mole of the arylidenemalonic ester in 500 cc. of 95% ethanol. The mixture was heated to boiling and allowed to stand. Separation of the product usually began within an hour. After standing overnight the solid cake was broken up, filtered, washed with 100 cc. of cold ether, and recrystalized from the appropriate solvent. The yields ranged from 70% to 90%.

METHOD B. One equivalent of the amine was added to a mixture of 1 mole of aldehyde and 1 mole of malonic ester in 500 cc. of 95% ethanol. The mixture was heated to boiling and allowed to stand overnight. Isolation and purification of the products were carried out as in Method A.

TABLE II

Tetraethyl (α,α'-Diaryl-1,4-Piperazylene Dimethylene) Dimalonates

Aryl	M.P. C.	Recrystallizing solvent	Analysis % Calculated C	H	N	Found C	H	N
Phenyl	151-152	Toluene	65.9	7.3	4.8	66.1	7.2	4.9
3,4-Methylenedioxyphenyl	150-151	Toluene	60.7	6.3	4.2	61.0	6.5	4.2
o-Chlorophenyl	156-157	Benzene	..	.	4.3	..	..	4.3
p-Methoxyphenyl	146-147	95% ethanol	63.5	7.2	4.4	63.7	7.2	4.3
2-Furyl	126-127	95% ethanol	59.8	6.8	5.0	59.8	6.8	5.0

TABLE III

Diethyl α-(4-phenyl-1-Piperazyl) R-Malonates

Aryl	M.P. C.	Recrystallizing solvent	Analysis % Calculated C	H	N	Found C	H	N
Benzyl	144-145	95% ethanol	70.2	7.4	6.8	70.3	7.4	6.7
3,4-Methylenedioxybenzyl	144.145	95% ethanol	66.0	6.7	6.2	65.8	6.8	6.2
p-Methoxybenzyl	146-147	95% ethanol	68.1	7.3	6.4	68.2	7.4	6.4
2-Furfuryl	103-104	50% ethanol	66.0	7.1	7.0	66.1	7.1	6.9

Attempted Condensation with Cyanacetate

Piperazine hexahydrate, 19.4 g., was added to a mixture of 21.2 g. of benzaldehyde and 22.6 g. of ethyl cyanacetate in 100 cc. of 95% ethanol. The mixture was heated to boiling and allowed to stand overnight. The product of recrystallization from 95% ethanol melted at 50-51°. There was no melting point depression when mixed with an authentic specimen of ethyl α-cyano-βphenylacrylate.

Saponification of (I)

Ten grams of (I) was dissolved in 400 cc. of hot absolute ethanol and a solution of 5 g. of potassium hydroxide in 100 cc. of absolute ethanol was added. The mixture was refluxed for two hours. On cooling, 5.5 g. of a nitrogen-free salt separated in long needles. It was recrystallized from 95% ethanol and dried in a desiccator over phosphorous pentoxide. One gram of the salt was dissolved in 10 cc. of water and 1 cc. of 6 N hydrochloric acid added. No precipitate formed even after standing in the ice chest for several days. Two grams of the salt was heated to 120°, a loss in weight of 10% taking place. A small amount of distillate was collected and identified as ethanol by conversion into its napthylurethan, m.p. 79-79.5°. The heated portion of the potassium salt was dissolved in 15 cc. of water and treated with 2 cc. of 6 N hydrochloric acid. After standing overnight, crystals were obtained, melting at 196-197°, and were identical with an authentic sample of benzalmalonic acid. According to these reactions the original potassium salt was probably potassium α-ethoxybenzylmalonate.

The alcoholic mother liquor was treated with 15 cc. of concentrated hydrochloric acid. A precipitate formed immediately and was filtered off. The precipitate was dissolved in water, treated with 5 g. of sodium nitride and excess hydrochloric acid, and then heated to boiling. On cooling, 1,4-bis-nitrosopiperazine, m.p. 158° was deposited. The amount obtained accounted for 75% of the piperazine in the original molecule.

Attempted Formation of Barbiturate of (I)

Twenty grams of (I) was dissolved in 500 cc. absolute alcohol containing 2.5 g. dissolved sodium and 6 g. urea. The mixture was refluxed for several hours during which a yellowish powder separated from the solution. The solution was cooled and the powder filtered off. The mother liquor was acidified with hydrochloric acid and the alcohol removed by evaporation. The residue was dissolved in water, treated with 5 g. sodium nitrite and excess hydrochloric acid and then heated to boiling. On cooling 1,4-bis-nitrosopiperazine, m.p. 158°, was deposited in almost theoretical quantity.

The yellowish powder lost ethanol on warming and the residue appeared to be benzalbarbituric acid but the product was not further investigated.

Hydrogenolysis of (I)

One hundred grams of (I) was placed in a hydrogenation bomb with 250 cc. of dioxane and 6 - 8 g. of Raney nickel. Hydrogen at 1000 lb./sq. in. (68 atm.) pressure was used. No absorption of hydrogen took place at room temperature even after shaking for ten hours. The temperature was raised gradually to 100° where hydrogen absorption was fairly rapid. After approximately 2 moles of hydrogen per mole of (I) had been absorbed the shaking was stopped and the apparatus allowed to cool. From the dioxane solution, after filtration from the nickel, the following products were isolated and converted to suitable derivatives for identification: 3 g. of piperazine, 4.5 g. of malonic ester, 5 g. of dibenzylpiperazine and 31 g. of benzylmalonic ester.

SUMMARY OF PART I

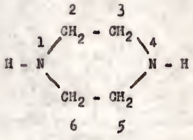
A number of amine addition products to conjugated systems have been prepared and their properties studied. Addition products of this type appear to be too unstable for use in further syntheses.

PART II

SYNTHESIS OF SUBSTITUTED PIPERAZINES

Introduction

Piperazine (diethylenediamine or hexahydropyrazine) is a heterocyclic di-secondary amine with the structure indicated. The ring is numbered clockwise starting with one nitrogen atom.



There are several general methods of synthesizing the piperazine ring.

1. Reaction of ammonia or primary amine with a 1, 2-halogenated alkane. Piperazine itself may be prepared by heating alcoholic ammonia and ethylene dichloride or dibromide in a sealed tube.[28] Similarly, 1, 4-diphenylpiperazine is obtained by heating ethylene bromide and aniline in be presence of sodium carbonate.[29]

2. Reduction of a pyrazine. 2-Methylpyrazine yields 2-methylpiperazine on reduction with sodium in alcohol.[30]

3. Heating a β-bromalkylamine. 1, 4-dibenzyl piperazine is formed by heating β-bromethylbenzylamine with excess alkali.[31]

4. Reduction of a diketopiperazine with sodium in alcohol

or by catalytic reduction over copper chromite in dioxane solution at 250°. Thus, 2,3-diketo piperazine may be reduced to piperazine by use of sodium in anhydrous amyl alcohol[32] or by use of zinc and aqueous alcoholic sodium hydroxide[32] and 2,5-diisobutyl-3,4-diketopiperazine yields 2,5-diisobutylpiperazine on catalytic reduction.[33]

5. N-Aryl piperazines are obtained by refluxing an aromatic amine with a bis (β-halogeno ethyl) amine in butanol solution in the presence of sodium carbonate. N-Phenyl piperazine is prepared in this manner from aniline and bis (β-bromethyl) amine.[34]

6. N-Phenylpiperazine may be prepared by heating a mixture of aniline hydrochloride and diethanolamine hydrochloride to 240-250° for several hours.[35]

There are a great many modifications of these methods but the examples cited are typical methods of ring closure for preparation of piperazine derivatives.

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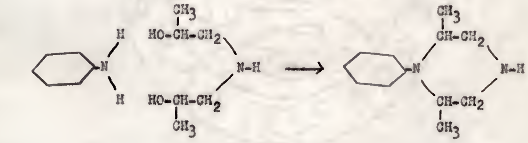
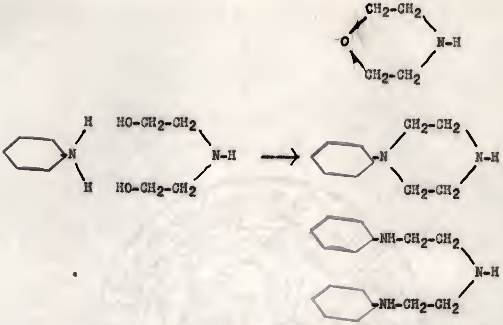
Attempted Synthesis of 1-Phenyl-2,6-dimethylpiperazine

Of the methods of ring closure given, the synthesis of Pollard and MacDowell[35] is perhaps one of the most interesting since both aniline and diethanolamine are cheap and commercially available. It was the original purpose of this investigation to extend this method of synthesis to the 1-Aryl-2,6-dimethylpiperazines.

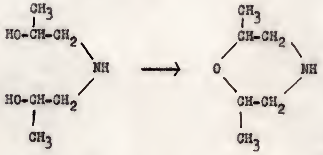
It was expected that by heating a mixture of aniline and diisopropanolamine hydrochlorides under conditions similar to those used in the synthesis of N-phenylpiperazine that 1-phenyl-2,6-dimethylpiperazine (cis and trans forms) would be obtained.



It should be pointed out that the synthesis of N-phenylpiperazine is complicated by the formation of numerous by-products such as morpholine and bis-(β-phenylaminoethyl)-amine,[35] as well as compounds of unknown constitution.



The reaction is by no means clear-cut and has not been studied sufficiently. This fact was fully realized when the synthesis of 1-phenyl-2,6-dimethylpiperazine from diisopropanolamine and aniline was attempted. The only products identified from the reaction product were 2,6-dimethylmorpholine and unreacted aniline. The morpholine was formed by cyclization of diisopropanolamine.



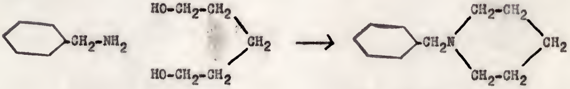
Several other fractions were obtained which appeared to be pure compounds but they were not identified. A fractional distillation of the reaction mixture is recorded in Table V with the pure fractions marked with an asterisk. Careful work with larger quantities of materials should yield interesting results; however, since this method is apparently not particularly applicable to the synthesis of alkyl piperazines it was not further investigated.

Catalytic Alkylation of Amines and its Application to Synthesis of Piperazine Derivatives

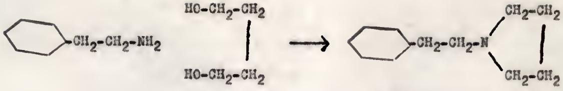
Quite recently, Adkins[36,37] and co-workers have developed a technique for the catalytic alkylation of amines by alcohols. In their papers, the reaction of equimolecular amounts of a glycol and a primary amine to yield piperidines, pyrrolidines, and hexahydroazepines is described.

The amine and glycol were dissolved in 600 to 800 cc. of dioxane and 30 to 60 g. of a copper-chromium oxide catalyst[51] was added. This mixture was placed in a hydrogenation bomb under 200 to 400 atmospheres of hydrogen. After heating for one hour at 250° the contents of the bomb was filtered from the catalyst and the dioxane removed by distillation at atmospheric pressure. The residue was then fractionated under vacuum to separate unused amine and glycol from the desired alkylated amine.

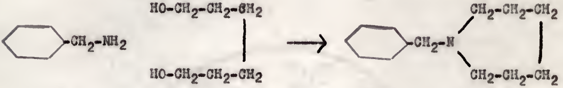
Typical compounds used and products obtained are indicated by the following equations:



1-benzylpiperidine

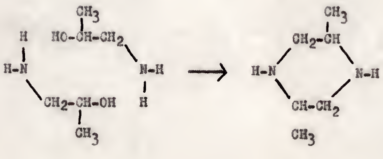


1-phenethylpyrrolidine

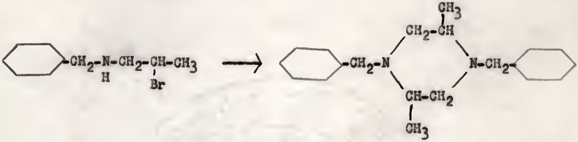


1-benzylhexahydroazepine

It appeared from this work that if the method were general, substituted piperazines could be prepared from commercially available starting materials. By an intermolecular reaction two molecules of isopropanolamine should yield 2,5-dimethylpiperazines. This was found to be the case. By use of approximately the same conditions as used by Adkins, this piperazine was prepared in 20% yield. Since 2,5-dimethylpiperazine is a disubstituted six membered ring it exists in cis and trans forms. Only the trans form was isolated in this investigation. Stoehr[38] had previously prepared trans 2,5-dimethylpiperazine by reduction of 2,5-dimethylpyrazine with sodium and alcohol.

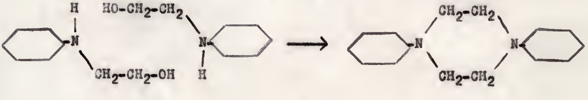


Uedinck[49] prepared a 1,4-dibenzyl 2,5-dimethylpiperazine, m.p. 105-106°, by the condensation of two molecules of N-β-brompropyl-N-benzylamine in the presence of alkali.

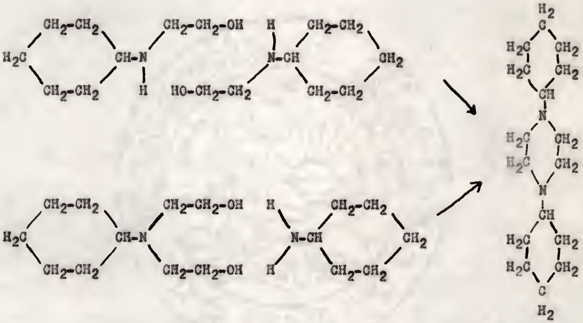


This compound is probably the trans form. It seemed of interest to synthesize a known specimen of 1,4-dibenzyl-trans-2,5-dimethylpiperazine and compare its melting point with that of Uedinck's compound. The known specimen was prepared by alkylating trans-2,5-dimethylpiperazine with benzyl chloride and melted at 108.5-109°. The experiment was inconclusive since Uedinck had only a very small sample at his disposal and may have not obtained it in a pure condition. On the other hand, it might be the cis form though this is unlikely since most syntheses of a dialkylpiperazine yield mainly the trans form.

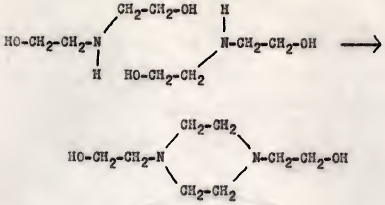
Similarly, two molecules of N-phenylethanolamine condense to form 1,4-diphenylpiperazine in 50% yield.



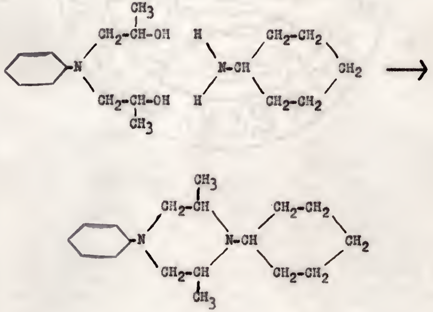
1,4-Dicyclohexylpiperazine was prepared in two ways: by the first method, two molecules of N-cyclohexylethanolamine condensed to form the piperazine and by the second, equimolecular quantities of N-cyclohexyldiethanolamine and cyclohexylamine formed the piperazine.



Piperazyl-1,4-bis-β-ethanol has been prepared by alkylating piperazine with ethylenechlorhydrin[39] and with ethylene oxide.[40] It does not appear to have been prepared from diethanolamine directly. This cheap commercial amino-alcohol readily yielded the piperazyl-alcohol on catalytic alkylation in 20% yield.



Cyclohexylamine was alkylated by N-phenyldiisopropanolamine to yield 1-cyclohexyl-2,6-dimethyl-4-phenylpiperazine in 20% yield. This compound should exist in cis and trans forms. Its configuration was not established, although it is probably trans.



During the fractionation of the reaction mixtures obtained in preparing 1,4-dicyclohexylpiperazine by both methods a fraction boiling at 60-61° at 10 mm. was obtained. This fraction was identified as cyclohexanol. An experiment was carried out to see whether this alcohol could be obtained by heating a dioxane solution of cyclohexylamine and water with copper chromium oxide catalyst. A yield of about 25% crude cyclohexanol resulted. Such a reaction has not been previously reported by workers in the field of high pressure catalytic reactions and is of considerable interest. Cyclohexanol was not obtained on heating cyclohexyl amine, water and dioxane in the absence of the catalyst. If the action is general with other amines, the low yields in some catalytic alkylations may be accounted for in part. The only water present in the alkylation mixture is that produced by the alkylation. This reaction should be further investigated as to its generality and applicability.

EXPERIMENTAL

Preparation of Intermediates

ISOPROPANOLAMINES These compounds have been prepared previously, 41,42,43,44, usually from propene oxide and ammonia. Since propene oxide is now commercially available, this method is desirable. The reaction of propene oxide and ammonia proceeds with formation of all three isopropanolamines. No particular conditions suitable for formation of one amino-alcohol to the exclusion of the others were sought as all three were desired.

Eight liters of concentrated ammonium hydroxide was placed in a twelve liter flask equipped with condenser, mercury-sealed stirrer, dropping funnel and thermometer. Propene oxide was added in 500 g. portions. There was a slight exothermic reaction so that cooling was necessary. The temperature was maintained at 20 to 27° in order to minimize loss of the oxide. After each addition of the oxide the mixture was stirred for about an hour during which the temperature rose from 20° to 27° and gradually dropped back to 20°. A total of 2800 g. propene oxide was added and the mixture allowed to stand overnight. Water and ammonia were removed by distillation through a five foot packed column using a total condensation-part takeoff head. When the temperature of the distillate reached 150° the mixture was cooled and distillation completed at 10 mm. A fraction of 856 g. of isopropanolamine boiling at 60° was collected followed by 1538 g. diisopropanolamine, b.p. 132°, and 600 g. triisopropanolamine b.p. 171-173°. Isopropanolamine is a liquid at room temperature while the other two are solids. Diisopropanolamine was refractionated, b.p. 132° at 10 mm., and collected in three fractions m.p. 39.6°, 39.5° and 39.2° respectively. Carbide and Carbon Chemicals Corporation[41] report m.p. 32° for diisopropanolamine and 45° for triisopropanolamine.

N-PHENYLETHANOLAMINE was purchased from Carbide and Carbon Chemicals Corporation. It was redistilled, the fraction used boiled at 149.5° at 10 mm..

N-CYCLOHEXYLETHANOLAMINES were prepared by passing ethylene oxide into a methanol solution of cyclohexylamine. There is a slight exothermic reaction. A pressure bottle might be used to good advantage to prevent loss of ethylene oxide. The amino-alcohols were distilled at 10 mm. pressure. N-Cyclohexylethanolamine boils at 118° at 10 mm. and N-cyclohexyldiethanolamine at 175° at the same pressure. Since these compounds were new, their neutral equivalents were run. N-cyclohexylethanolamine, N.E. calculated 143.2, found 143.0. N-cyclohexyldiethanolamine, N.E. calculated 187.3, found 187.2 As a further check densities and refractive indices were determined and the calculated molecular refractions compared with the experimental (using Lorenz and Lorentz equation: $MR = \frac{M}{D} \cdot \frac{n^2-1}{n^2+2}$). N-Cyclohexylethanolamine $D_{20}^{24} = 0.9788$ $N_D^{25} = 1.4842$, MR calculated 42.07 (atomic refractions used were those of Auwers and Eisenlohr[45]), found 41.89. N-Cyclohexyldiethanolamine,

D_{20}^{24}=1.003, N_D^{25}=1.4927, MR calculated 53.17, MR found 52.68.

DIETHANOLAMINE was the purified commercial product, b.p. 148.5° at 10 mm.

N-PHENYLDIISOPROPANOLAMINE was prepared by heating one mole of aniline and two moles of propene oxide dissolved in 200 cc. dioxane to 170° under 600 lbs. hydrogen pressure for 4-5 hours. After removal of low boiling fractions N-phenyldiisopropanolamine distilled at 184-5° at 10 mm.. The yield was about 90%. It was a viscous, straw-colored liquid which did not solidify even on standing in the ice chest for several weeks. N calculated 6.69, N found 6.60.

N-p-TOLYLDIISOPROPANOLAMINE was prepared in the same manner as N-phenyldiisopropanolamine. After removal of low boiling products the residue solidified on cooling; it was recrystallized several times from hexane or diisopropylether in slightly pink needles m.p. 112°; N. calculated 6.27 N., found 6.20.

TABLE IV

Boiling Points of Intermediates

Compound	Experimentally Determined B. P. at 10 mm.	B.P. Literature	Pressure
Aniline	70		
Isopropanolamine	60	45(41)	5
Diisopropanolamine	132	116(41)	5
Triisopropanolamine	171	144(41)	5
Diethanolamine	148.5	144(41)	10
N-Phenylethanolamine	149.5		
N-Phenyldiisopropanolamine	184-5		
N-Cyclohexylethanolamine	118		
N-Cyclohexyldiethanolamine	175		

Alkylation of Aniline with Diisopropanolamine

The general procedure was originated by Pollard and MacDowell.[35] A mixture of five moles of aniline and five moles of diisopropanolamine in a five liter, three-necked flask equipped with an air condenser, mercury-sealed stirrer and thermometer was treated with one liter of concentrated hydrochloric acid. The heating was accomplished by a transformer-controlled heating unit wound on the outside of the flask. The stirrer was started and the mixture heated. After the distillation of water and excess hydrochloric acid, the temperature was raised to 245-255° and the fused hydrochlorides held at this temperature for four to five hours. During this heating period further hydrochloric acid and water distilled.

The mixture on cooling solidified to a hard mass. It was treated with excess 40% sodium hydroxide. After standing a day the hydrochlorides had decomposed and a heavy, dark oil floated on the surface. The oil was separated and the aqueous solution extracted with benzene. The oil and benzene extracts were combined and dried over flake sodium hydroxide. After drying several days, the solution was filtered and distilled through a three foot column packed with 6 mm. Rasching rings. All heating was done electrically. The still head was of the total condensation-part takeoff type.

The first fraction consisted of benzene and water. The second was 2,6-dimethylmorpholine boiling mainly from 143° to 147°. This compound should exist in cis-trans forms but isolation of these isomers has not been reported in literature. The compound has been reported in patent literature[50] as boiling at 145°. Krasuskii[44] prepared 2,6-dimethylmorpholine from diisopropanolamine and reported the boiling point 144° and D 0.935. The physical constants of the product prepared in this research were in fair agreement with the work of previous investigators.

Unused aniline was the only other product identified from the reaction mixture. The fractions marked with an asterisk appeared to be fairly pure but since they did not appear to be the desired product, they were not further investigated.

TABLE V

Fractionation of Reaction Product from Aniline and Diisopropanolamine (5 moles each)

B. P.	Pressure	Weight	N_D^{20}
140.0-142 m	atm.	6	1.4450
142.0-143 m	atm.	14	1.4454
143.0-145 m	atm.	55	1.4454
145.0-146.8 m	atm.	76	1.4458
146.8-148 m	atm.	16	1.4465
68.0-82	62	7	1.4486
82.0-91.5	62	3.5	1.4540
91.5-101	62	2	1.4873
101.0-105.5 a	62	5	1.5329
105.5-107 a	62	5	1.5785
107.0-107.1 a	62	32	1.5835
68.5 a	10	110	1.5844
68.5-72 a	10	9	1.5805
72.0-98	10	7	1.5478
98.0-104	10	18.5	1.5470
104.0-104.2*	10	16	1.5523
104.2-109	10	8	1.5523
109.0-120	10	7	1.5498
120.0-129	10	14.5	1.5506

TABLE V (Continued)

B. P.	Pressure	Weight	N_D^{20}
129.0-130.5*	10	45	1.5510
130.5 *	10	13	1.5514
130.5-131*	10	25	1.5512
131.0-134	10	11	1.5543
134.0-139	10	10	1.5610
139.0-140	10	10	1.5646
140.0-142.5	10	6.5	1.5680
142.5-145*	10	45	1.5642
145.0-153	10	25	1.5630
143.0-159	10	8	1.5606
110.0-129	4	15	1.5953
129.0-134	4	8	1.5884
134.0-142	4	6	------
142.0-147.5	4	2	1.5663
147.5-162.5	4	10	1.5779
162.5-166.5	4	17	------
166.5-175	4	28	------

m 2,6-dimethylmorpholine

a aniline

* fairly pure fractions, not identified

Piperazines by Catalytic Alkylation

Trans -2,5-dimethylpiperazine

Seventy-five grams (one mole) of isopropanolamine was dissolved in 350 cc. dioxane. This mixture was placed in a bomb with 15 g. copper-chromium oxide catalyst.[51] The bomb was heated under a pressure of 500 lbs. hydrogen per sq. in. to 250-275° for 5 hours. After cooling overnight the bomb was opened and the catalyst filtered from the dioxane solution. The clear solution was then fractionated through a two foot column to remove dioxane and low boiling materials. When the temperature of the distillate reached 105° the distillation was discontinued; the residue was transferred to a Claisen flask and distillation continued. The fraction boiling 160-175° solidified on cooling and was recrystallized from hexane, m.p. 115°, yield 18%. The reported value from literature[38] was 117°.

The identity of the compound was extablished by converting it to the 1,4-dinitrosopiperazine,[47] m.p. 174°, by treating it with sodium nitrite and dilute hydrochloric acid. Further identification was made by preparation of 1,4-dibenzoyl- trans-2,5-dimethylpiperazine[48] m.p. 228-229°. No cis-2,5-dimethylpiperazine was isolated.

1, 4-Dibenzyl-trans 2, 5-dimethylpiperazine

This compound was obtained by refluxing a mixture of trans2,5-dimethylpiperazine and excess benzyl chloride with 10% sodium carbonate for several hours. The oily layer was steam distilled to remove excess benzyl chloride. On cooling, it solidified. After filtration and washing with water it was recrystallized from methanol in platelets melting at 105-106°. Further purification raised the melting point to 108.5-109°. It is probably identical with the 1,4-dibenzyl-2,5-dimethylpiperazine of unknown constitution prepared by Uedinck[49] from N-β-brompropyl,N-benzylamine.

The compound was converted to the hydrobromide by treating it with excess hydrobromic acid. The product was readily recrystallized from dilute hydrobromic acid. After drying over sodium hydroxide it was analyzed by titration. This was possible since the hydrobromide was soluble and the free base insoluble in water. Using phenolphthalein as the indicator the neutral equivalent was found to be 227.4. The calculated value is 228.1.

Piperazyl-1,4-bis-β-ethanol

The bomb was charged with 75 g. diethanolamine, 350 cc. dioxane and 20 g. copper-chromium oxide catalyst. It was heated to 250-275° under 500 lbs. per sq. in. hydrogen pressure for four hours. After the bomb had cooled it was opened. A slight odor of ammonia was noticeable. The catalyst was removed by filtration and the dioxane distilled. A small amount of material boiling below 145° at 3 mm. was thrown away. The fraction 145-155° at 3 mm. solidified on cooling. Higher boiling fractions remained as viscous, colored liquids. The solid fraction was recrystallized from absolute ethanol and melted at 134-135°. Pyman[39] reports 134-135° as the melting point of this product. The compound was further identified by converting it to the dibenzoate with benzoyl chloride and sodium hydroxide. After recrystallization from methanol it melted at 104.5-105°. Pyman reports the melting point of Piperazyl-1,4-bis-β-ethyl benzoate as 104-105°.

1,4-Diphenylpiperazine

The preparation of this compound was accomplished in the manner previously described for the other alkylations. The compound partially crystallized from the dioxane solution after filtration. A further quantity was obtained on concentrating the mother liquor. The total yield of crude product amounted to 55%. One recrystallization from ethanol was sufficient to give a product melting at 163.5-164.5°. A mixed melting point with an authentic sample of 1,4-diphenylpiperazine prepared by the method of Bischoff[29] showed no depression.

1-Cyclohexyl-2,6-dimethyl,4-phenylpiperazine

Equimolecular quantities of cyclohexylamine and N-phenyldiisopropanolamine were reacted in the usual manner. A large amount of material boiling below 205° was collected. The desired product distilled at 205-210° at 2 mm. The crude yield amounted to 20%. In order to purify the compound it was converted to the dihydrobromide by hydrobromic acid. Impurities such as amino alcohols and considerable colored material remained dissolved in the excess hydrobromic acid. The solid dihydrobromide was washed several times with acetone and alcohol and dried.

The dihydrobromide was used for analysis. N.calculated 6.45, found 6.41; Br calculated 36.81, found 36.83 (gravimetric).

1,4 Dicyclohexylpiperazine

METHOD A. N-Cyclohexylethanolamine was reacted under the usual aklylation conditions. The resulting mixture was fractionated through a twenty inch column. After removal of dioxane at atmospheric pressure, the pressure was reduced to 10 mm. Two low-boiling fractions were collected at this pressure, one at 60-61° and the other at 104-110°. The fraction boiling between 170° at 10 mm. and 200° at 5 mm. partially solidified on cooling. This fraction was dissolved in pentane at room temperature and cooled in an ice-hydrochloric acid bath. The crystalline 1,4-dicyclohexylpiperazine which separated was recrystallized from aqueous methanol. The product melted at 118°.

For analysis, the compound was converted to the dihydrobromide by excess hydrobromic acid. The dihydrobromide was recrystallized from dilute hydrobromic acid and analyzed for bromine gravimetrically. Calculated Br. for 1,4-dicyclohexylpiperazine dihydrogromide 38.77, found 38.76, 38.77. The neutral equivalent was also determined by titration of the dihydrobromide with standard alkali using phenolphthalein as the indicator. It was necessary to add benzene to the titration flask to remove the free base as it was formed during the neutralization. N.E. calculated 206, found 208.

The fraction boiling at 60-61° was made acid to methyl orange and the mixture extracted with ether. On distillation through the twenty inch column this neutral fraction boiled at 60° at 10 mm. It was identified by its physical constants (density, boiling point, and refractive index) as cyclohexanol. Treatment of this fraction with phenylisocyanate yielded a phenylurethane m.p. 82.5°.A mixed melting point with authentic cyclohexylphenylurethane showed no depression. Similarly the α-napthylurethane of the unknown, m.p. 128.5-129° showed no depression of the melting point on mixing with an authentic sample of cyclohexyl-α-napthylurethane, m.p. 128.5-129°.

The second low boiling fraction was not identified.

1,4 Dicyclohexylpiperazine

METHOD B. Equimolecular quantities of cyclohexylamine and N-cyclohexyldiethanolamine were reacted under the usual conditions. After filtration of the reaction mixture the solution was fractionated through a twenty inch column. Two low-boiling fractions were obtained from this reaction also. They appeared to be identical with those obtained in METHOD A. The fraction boiling at 60-61° was identified as cyclohexanol. The third fraction solidified as in METHOD A and was purified in the same manner. The recrystallized product melted at 118° and showed no melting point depression on mixing with the 1,4-dicyclohexylpiperazine prepared by METHOD A. The yield was about 20%.

Formation of Cyclohexanol from Cyclohexylamine

The bomb was charged with 60 grams cyclohexylamine (b.p. 134°), 300 cc. dioxan (b.p. 100-101°), 20 grams of water and 20 grams of copper-chromium oxide catalyst. It was heated at 260-270° for four and one-half hours under a pressure of 500 lbs. per sq. in. of hydrogen. On opening the bomb a distinct odor of ammonia was noticed. The dioxane solution was fractionated through a twenty inch column. A crude yield of about 15 grams of cyclohexanol boiling at 60-61° at 10 mm. was obtained. The purified cyclohexanol yield amounted to 18% of the theoretical. It was identified by its refractive index and as its phenylurethane.

A second fraction boiled 108-114° at 10 mm. and partially solidified on cooling. It was not identified.

SUMMARY

A number of substituted piperazines were prepared from commercially available starting materials by high pressure catalytic alkylation. The method seems to be a general one and should be extended. During the catalytic alkylation process a number of by-products are formed. A study of these by-products should bring to light new reactions. An example of this is the isolation of cyclohexanol from cyclohexylamine and its derivatives under catalytic alkylation conditions. A reaction of this type has not been previously reported.

Although high yields have not been obtained, the technique can undoubtedly be improved to give more satisfactory results.

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BIOGRAPHICAL ITEMS

Joseph Paul Bain was born May 3, 1914, in Richmond, Virginia. He attended the public schools of Richmond, Virginia; Dunnellon, Florida; and Gainesville, Florida, and was graduated from the University of Florida in 1935 with the degree of Bachelor of Science with honors. He has attended the University of Florida continuously from the fall of 1931 to the present.

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COMMITTEE REPORT

This dissertation was prepared under the direction of the Chairman of the candidate's Supervisory Committee and has been approved by all members of the Committee. It was submitted to the Graduate council and was approved as partial fulfilment of the requirements for the degree of Doctor of Philosophy.

Date May 29, 1939

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